Remarks

Applicants have amended claims 16 and 17 to a preferred embodiment, namely to an embodiment, wherein the enrichment of the fetal nucleic acid is accomplished by using an enzyme that selectively and substantially completely digests the maternal nucleic acid from the treated sample. Support for the amendment can be found throughout the specification and claims, for example, claim 1. Accordingly, no new matter has been introduced by the amendment and its entry is respectfully requested. Applicants have added new claims 22 and 23. Support for these claims can be found, for example in claim 5. Accordingly, no new matter has been introduced by the new claims and their entry is respectfully requested.

Applicants now turn to the specific rejections.

The Examiner rejected claims 16 and 17 under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 6,927,028 ("'028 patent"). Specifically, the Examiner alleged that Figure 4 of the '028 patent "teaches bisulfite treatment to the plasma sample from a pregnant woman and this step is considered the same as enriching fetal nucleic acids region in the plasma sample since this step removes (converts methylated cytosine to uracil) the maternal DNA, thus enriching unmethylated fetal DNA intact."

Although Applicants respectfully disagree, Applicants have amended claims 16 and 17 to explicitly refer to a method whereby the fetal nucleic acid is enriched, namely, by enzymatic digestion. The '028 patent does not teach or suggest using an enzyme to enrich the fetal nucleic acid. Accordingly, because the '028 patent does not disclose all the elements of claims 16 and 17 the rejection has been rendered moot.

Accordingly, Applicants respectfully submit that the rejection of claims 16 and 17 under 35 U.S.C. §102(e) is improper and should be withdrawn.

The Examiner rejected claims 1-15 under 35 U.S.C. 103(a) as allegedly being unpatentable over the '028 patent in view of U.S. Patent No. 7,348,139 ("the '139 patent"). Specifically, the Examiner alleged that the '028 patent teaches an "enrichment" step. The Examiner also argued that the '028 "bisulfite treatment to the maternal plasma as taught by Lo [the '028 patent] teaches a step of reducing or destroying the maternal DNA to enrich the fetal DNA in the maternal sample" (page 3 of February 2, 2009 Office Action). The Examiner further

argued that Herman further teaches that methylation can be detected with methylation sensitive enzymes and thus, the claims are obvious.

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

The present claims are specifically directed to enrichment of fetal nucleic acids using an **enzymatic digestion**. As discussed, *supra*, the '028 does **not enrich** the fetal nucleic acids **using an enzyme**. There is no motivation in the field to combine the '028 with the '139. Although the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007), stated that references did not have to have an explicit teaching that leads to the combination of references, the Court acknowledged that there had to be some motivation based upon the overall art. As explained below there is not such motivation. Moreover, the level of enrichment that can be obtained by enzymatic digestion compared to the bisulfite method is significantly, and unexpectedly higher.

Applicants submit as evidence of the unexpectedly superior results an article by Chan et al. (Clinical Chemistry, 2006, Exhibit A). Figure 3 at page 2215 of Exhibit A shows that after the enzyme digestion, the nucleic acid originating from the mother is substantially completely absent. In contrast, the analysis of the sequencing reactions in the '028 patent shows that a large majority of the sample comprised maternal nucleic acid and only a very minor component of fetal nucleic acid (see, Figures 3 and 4 of the '028 patent).

Therefore, the enzymatic digestion provides a superior method to enrich fetal nucleic acids in the maternal sample over the method described in the '028 patent.

Applicants further submit that the claims require that the maternal nucleic acid is digested "substantially completely". This is not what the '028 patent teaches or suggests. Nothing in the '139 patent indicates that enzymatic digestion would result in such a dramatic improvement in the methods for differentiating fetal nucleic acids from maternal nucleic acids. The '139 patent only teaches that SOCS-1 gene is methylated in cancer. The Examiner's allegation that the '139 patent "teaches enzymes that digest methylated maternal DNA, leaving unmethylated DNA alone" (page 4 of the February 10, 2009 Office Action), is incorrect. While the '139 patent describes using bisulfite ions and a subsequent sequencing reaction to **distinguish between**

cancer cells and normal cells, there is nothing that would teach or suggest using an enzymatic digestion step to **enrich fetal** or other **nucleic acids** in a maternal plasma sample or any other sample to allow more accurate analysis of a minority population of nucleic acids present in the sample.

Thus, not only is one element, the substantially complete digestion step, not present in the cited prior art but also there would have been no motivation based upon the results in '028 to switch from bisulfite treatment to enzymatic treatment to achieve such a dramatic improvement in results.

The specific problem of analyzing a sample using the relative amount of one nucleic acid over another is that one easily misses or misinterprets the results for the minority nucleic acid population, which in this case represents the fetal nucleic acids in the maternal sample. This is recognized as a serious issue in connection with prenatal diagnostic methods and is also discussed in Exhibit A. The present application provides a significantly improved method by using enzymatic digestion, as opposed to a method that uses bisulfite, to substantially completely remove the maternal nucleic acids in a sample while minimizing the degradation of the low copy number fetal nucleic acid to make the fetal nucleic acid analysis much more reliable.

In view of the above, Applicants also submit that the invention is not obvious and further, provides unexpected superiority to the methods of the '028 patent. A skilled artisan could not have envisioned that by combining the '028 with the '139 one would have made the method of analysis of fetal nucleic acid from a maternal sample so much more superior.

Certainly, there is nothing that teaches the unexpected superiority of claims 5, 6, 7, 8-15, 22 and 23 using a methyl-sensitive enzyme.

Accordingly, Applicants respectfully submit that the rejection of claims 1-15 under 35 U.S.C. 103(a) as allegedly being unpatentable over the '028 patent in view of the '139 patent is improper and should be withdrawn.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance.

In the event that any additional fees are required, the Commissioner is hereby is authorized to charge our deposit account No. 50-0850. Any overpayments should also be deposited to said account.

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Respectfully submitted,

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